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(71) Applicants Instrumentation Laboratory Inc., 113 Hartwell Avenue, Lexington, Massachusetts 02173, United States of America
(72) Inventors Thomas F. Kelley, Ching Chiang
(74) Agents J. A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU

(54) **Analytical device**

(57) A unitary analytical device has a support structure (10) for manual manipulation, the structure defining a self-filling metering channel (16), and laminate structure (40) including a reagent layer (44) and a filter layer (42) on one side of the reagent layer. The self-filling channel (16), of capillary dimension, accurately meters and positions a minute quantity of liquid to be analyzed adjacent the reagent layer (44) and the filter layer (42) allows a portion only of the liquid to flow into fluid contact with the reagent material in the reagent layer for reaction therewith. The analytical device, with a single step of merely touching the metering channel inlet to a drop of the liquid, automatically meters a precision quantity of the liquid and distributes that quantity in a reaction region immediately adjacent the reagent material for reaction therewith.

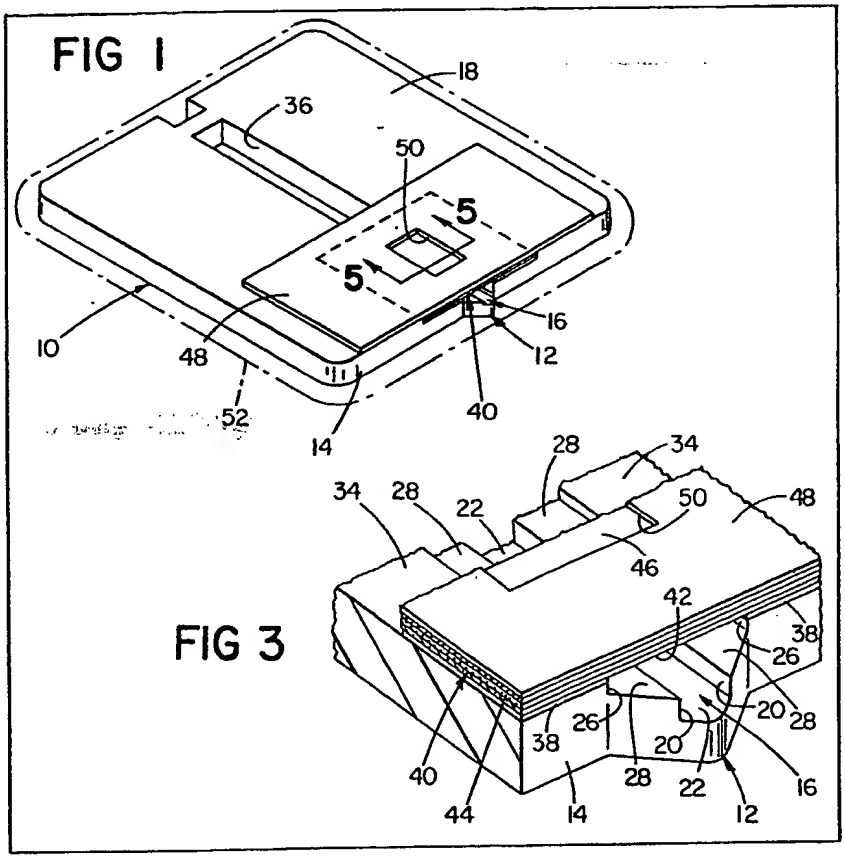


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FIG 1

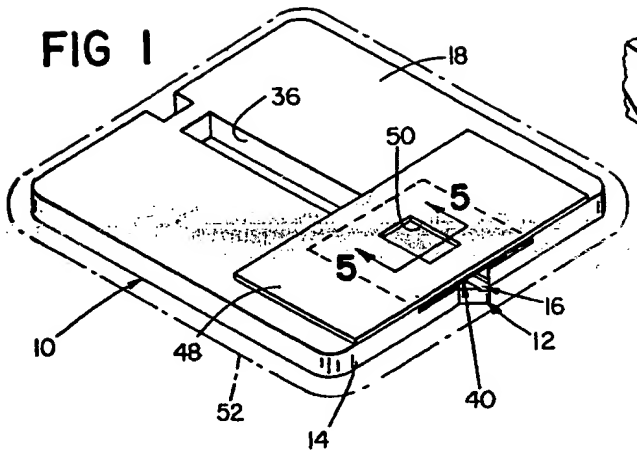



FIG 3

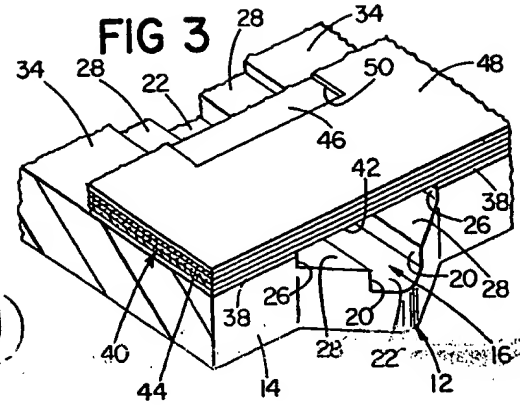
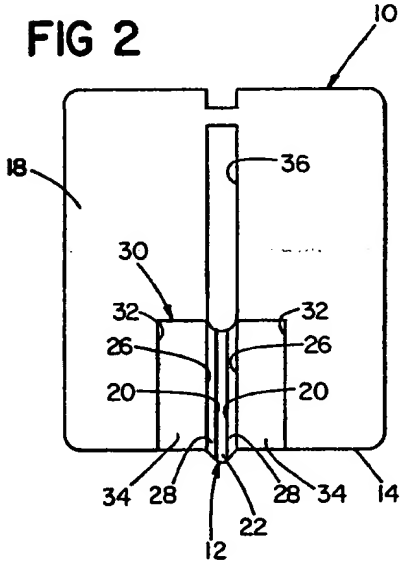



FIG 2



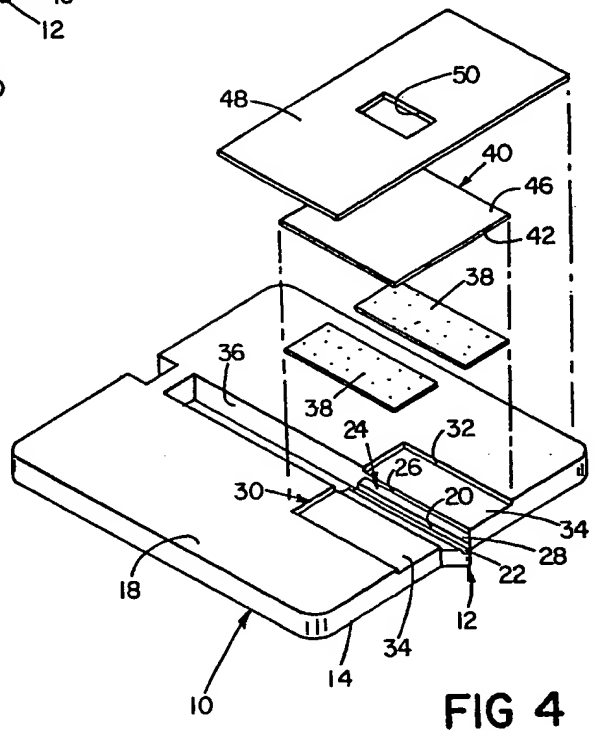




FIG 4

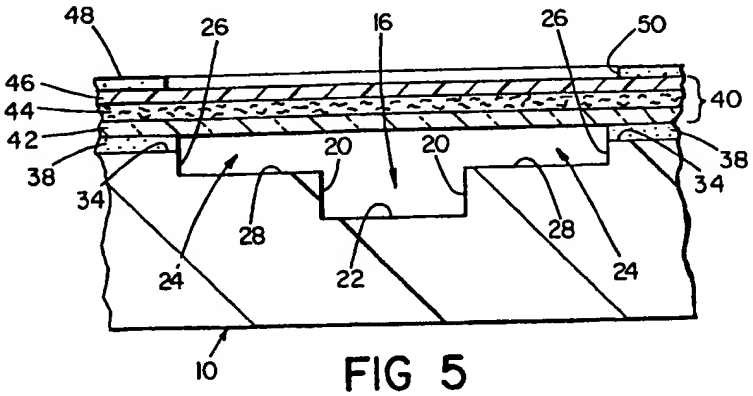



FIG 5

FIG 6

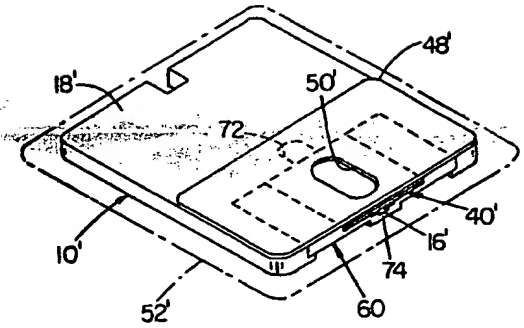



FIG 7

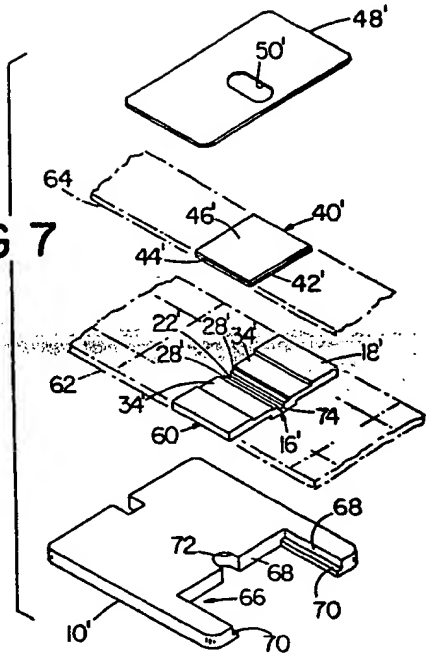



FIG 8

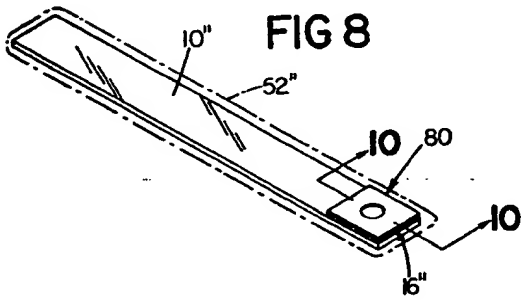
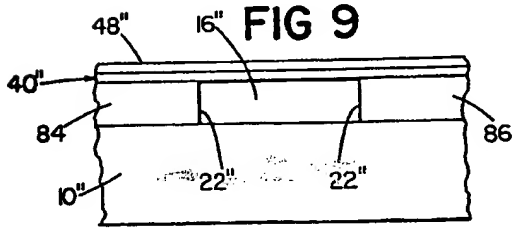



FIG 9



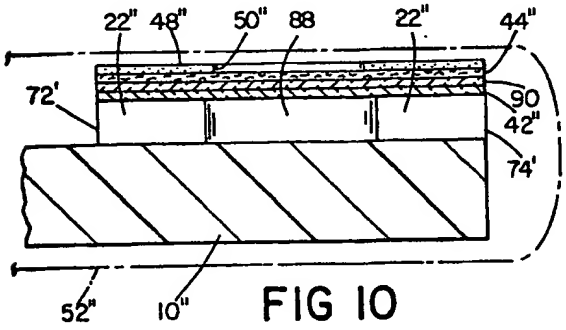




FIG 10

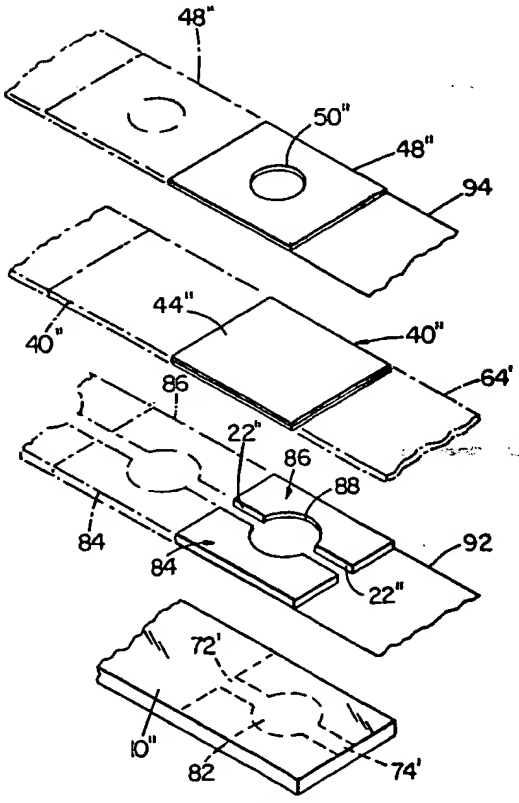



FIG 11

SPECIFICATION

**Analytical device**

This invention relates to analytical chemistry and more particularly to improved analytical devices for analysis of liquids and particularly biological fluids such as blood.

Numerous liquid analysis systems are known. Automated systems for carrying out chemical analysis of biological fluids, and especially the quantitative analysis of blood, have proved particularly advantageous in clinical laboratories. Some such systems mix the sample to be analyzed with bulk diluents and reagents for analysis; while other analytical systems employ reagent carrier elements on which a sample of the liquid to be analyzed is deposited. Examples of the latter type of system are shown in U.S. Patent 3,552,928 and U.S. Patent 4,042,335.

There is need for improved analytical devices which utilize small quantities of liquid and require minimal manipulative processing steps. Also, in the case of whole blood, analytical difficulties may arise due to the presence of constituents which may seriously interfere with the analysis.

In accordance with the invention there is provided a unitary single use analytical device that includes support structure for manual manipulation, structure defining a self-filling metering channel, and laminate structure including a reagent layer and a filter layer on one side of the reagent layer. The metering channel is in fluid communication with the reagent material through the filter layer is bounded in part by the support structure and in part by the filter layer and the reagent layer comprises reagent material in a supporting matrix, the reagent material being specifically reactable with the constituent of interest in the fluid to be analyzed. The analytical device, with a single simple step of merely touching the metering channel inlet to a drop of the liquid, automatically meters a precision quantity of the liquid and distributes that quantity adjacent the reagent material, and the filter layer allows a portion of the liquid to flow into fluid contact with the reagent material for reaction therewith.

In use for whole blood analysis, a blood sample to be analyzed is obtained simply by touching the inlet end of the metering channel to a drop of blood, the blood being drawn into the metering channel through capillary action, thus providing convenient and rapid metering of a sample of precise volume (less than ten microliters) from a drop of blood in less than ten seconds. The filter layer retains red blood cells in the metering channel and allows only the plasma or serum portion to contact the reagent layer, thus minimizing the hematocrit effect, i.e., the effect of red cells. The resulting detectable change in the reagent layer is sensed on the opposite side of the device and is measured, usually by suitable spectophotometric apparatus. In a particular embodiment, the intensity of color developed from the specific reaction between the chemical reagent component and a constituent of interest in the blood is measured by reflection densitometry while another embodiment reflection fluorescence is used to measure the detectable change.

In particular embodiments, the metering channel of the analytical device is formed with a vent port at the end of the channel opposite its inlet end so that air escapes from the channel as sample liquid flows into the channel; the support structure is a transparent substrate so that the sample liquid in the metering channel may be visually observed; the filter layer of the laminate structure includes a microporous membrane with pores of less than one micron size; a reflective surface is between the filter membrane and the reagent layer for reflecting a radiation beam incident on the reagent layers, and the reagent material comprises glucose oxidase, peroxidase, and an indicator composition comprising a compound oxidizable in the presence of hydrogen peroxide and peroxidase to effect formation of a dye. The laminate structure may also include a protective member in overlying relation to the reagent layer with a reagent viewing region therein. In a particular embodiment enhanced uniform distribution of plasma in the reagent layer is accomplished by elongated supplemental channel regions extending along the sides of the central metering channel.

Analytical devices in accordance with the invention can be adapted for carrying out a wide variety of chemical analyses, not only in the field of clinical chemistry but in chemical research and in chemical process control laboratories. In the field of blood analysis, for example, the analytical device can be adapted for use in carrying out quantitative analyses of many of the blood constituents which are routinely measured. For example, the device may be readily adapted for use in the analysis of such blood constituents as creatinine, lactic acid, urea nitrogen, glucose, as well as many other constituents, by appropriate choice of reagent or other interactive materials. Accordingly it will be appreciated that numerous different analytical devices, depending on the particular analysis, can be prepared in accordance with the invention; such devices can be configured in a variety of forms; and particular devices can be adapted for different types of tests.

The invention enables accurate metering and positioning of a sample to be analyzed which may be obtained directly from the liquid source without any intermediate handling steps, the channel typically being filled in less than four seconds. The device distributes the sample uniformly in the metering area for exposure to reagent material and the position of the blood sample in the channel is visible through the support substrate. The filter membrane isolates the reagent layer from potentially interfering constituents such as cellular structures of the blood sample to be analyzed; and the metering channel may include adjacent regions to enhance distribution of constituents of the blood sample relative to a region of optical measurement.

The invention provides a simple and reliable chemical analysis system suitable for manual use in which a minute quantity of the liquid to be analyzed is accurately metered, filt red and positioned for reaction and measurement in a single simple manipulative step.

Other features and advantages of the invention will be seen as the following description of particular embodiments progresses, in conjunction with the drawings, in which:

Fig. 1 is a perspective view of an analytical device in accordance with the invention;

Fig. 2 is a plan view of the support component of the device shown in Fig. 1;

Fig. 3 is an enlarged perspective view of the sampling tip portion of the device of Fig. 1;

Fig. 4 is an exploded perspective view of components of the device of Fig. 1;

Fig. 5 is a sectional view taken along the line 5—5 of Fig. 1;

Fig. 6 is a perspective view, similar to Fig. 1, of another analytical device in accordance with the invention;

Fig. 7 is an exploded perspective diagrammatic view of components of the device shown in Fig. 6;

Fig. 8 is a perspective view of another analytical device in accordance with the invention;

Fig. 9 is an end view of the analytical device shown in Fig. 8;

Fig. 10 is a sectional view taken along the line 10—10 of Fig. 8; and

Fig. 11 is an exploded perspective diagrammatic view of components of the device shown in Fig. 8.

Description of Particular Embodiments

The analytical device shown in Fig. 1 includes a transparent support 10 of acrylic resin that has a thickness of about 1 1/4 millimeter, a width of about 2 1/2 centimeters, and a length of about 2 1/4 centimeters. Sampling tip 12 at the front wall 14 of substrate 10 is of triangular configuration and projects forward about one millimeter from front wall 14. Formed in substrate 10 and extending rearwardly from sampling tip 12 (as indicated in Figs. 2, 3, and 4) is a metering channel recess 16 that has a width of about 0.8 millimeter, a depth (from top surface 18 of substrate 10) of about 0.7 millimeter, and a length of about one centimeter. Metering channel recess 16, which defines a volume of about five microliters, is defined by side walls 20 (spaced about 0.8 millimeter apart) and bottom surface 22 (spaced about 0.7 millimeter below top surface 18); and auxiliary channels 24 that extend along either side of channel 16 are defined by side walls 26 (spaced about 2.2 millimeter apart) and lower surface 28 (spaced about 0.4 millimeter below top surface 18). Formed in the front portion of surface 18 is a recess 30 (defined by side walls 32 and bottom surface 34) that is about 0.9 centimeter on a side and has a depth of about 1/3 millimeter. Extending rearwardly, as an extension of channel 16, is a slot 36 that is about one centimeter in length.

Positioned in recess 30 by double-sided adhesive strips 38 is a laminate membrane 40 that includes, as indicated in Fig. 5, a filter layer 42, an intermediate reagent layer 44, and a transparent protective over layer 46. Opaque adhesive strip 48 overlies in protective relation and secures laminate assembly 40 in recess 30. Viewing window 50 (about 1/4 centimeter wide and 1/2 centimeter long) exposes the upper surface of transparent layer 46 over metering channel 16.

The components of laminate assembly 40 and of its several layers depend on the intended analytical use. In a particular embodiment for glucose analysis, filter layer 42 is a Millipore Corporation type VCWP filter membrane of about 74 percent porosity with a mean pore size of 0.1 micron and a thickness of about 0.1 millimeter. Reagent layer 44 includes in a gelatin matrix glucose oxidase, 4-amino antipyrine, 2-(N-ethyl-m-toluidino)-ethanol and peroxidase and is about 0.02 millimeter in thickness; and layer 46 is a polyester (polyethylene terephthalate) film of about 0.1 millimeter thickness. A gelatin-reagent mixture is deposited as a coating on film 46 and after smoothing, the filter membrane 42 is placed on top of the reagent layer 44 with the dull side of filter layer 42 facing reagent layer 44. The resulting laminate assembly 40 is secured in recess 30 by double-sided adhesive strip 38 and opaque strip 48.

In use, a drop of blood is obtained, for example, by pricking the finger tip or heel of a patient with a lancet, an analytical device is taken from its protective envelope 52, and the inlet port of its metering channel 16 at tip 12 is touched to the drop of blood. The blood is drawn into the metering channel 16 through capillary action, the channel typically being filled with blood within less than four seconds. The loaded analytical device is then incubated for a predetermined time. Plasma flows through filter membrane 42 to reagent layer 44 while that filter layer blocks flow of blood cells. As the blood dries, blood cells tend to migrate to the auxiliary distribution channels 24 and produce a more uniform distribution of plasma in the reagent layer. In layer 44, in principle, the glucose is first oxidized by glucose oxidase, resulting in a stoichiometric formation of hydrogen peroxide, which then produces a purple pigment by reacting with 4-amino antipyrine and 2-(N-ethyl-m-toluidino)-ethanol in the presence of peroxidase. The upper surface of filter layer 42 is reflective and support layer 46 is transparent. Thus, the developed color may be measured by a reflection densitometer, either manually or automatically, with the sensing beam of the densitometer directed through viewing window 50 for measurement of reagent layer 44. The system reads glucose concentrations in the range of 0 to 400 mg/dl.

A second form of analytical device is shown in Figs. 6 and 7. That analytical device has a support 10′ with a subassembly insert 60 of shape as shown in Fig. 7. That subassembly insert 60 is

severed from a strip subassembly that includes a strip base 62 of transparent acrylic plastic that has a width of about 1.6 centimeter and is formed with recess surfaces 22', 28' and 34' of configuration similar to that of the embodiment of Figs. 1—5. Secured on surfaces 34' of strip 62 by suitable securing means is a laminate reagent strip 64 that includes a transparent upper layer 46', a lower filter layer 42' and an intermediate reagent layer 44'. This subassembly strip of base 62 and reagent strip 64 is severed to provide a series of inserts 60, each having a length of about 0.9 centimeter.

Manipulating support 10' has a recess 66 defined by side walls 68 (spaced about 1.6 centimeters apart) and support surfaces 70 (each about one millimeter in width). Subassembly insert 60 is seated on support surfaces 70 and secured by overlying protective sheet 48' as indicated in Fig. 6. A vent port in communication with the end of metering channel 16' remote from its inlet end is provided by recess 72.

The analytical device shown in Figs. 6 and 7 is used in manner similar to that of the analytical device of Figs. 1—5, the inlet end 74 of metering channel 16' being touched to the drop of blood or other liquid to be analyzed and that liquid being metered into the channel by capillary action and positioned in alignment with viewing window 50' for interaction with the reagents in layer 44'.

Still another form of analytical device is shown at Figs. 8—11, That analytical device is housed in protective envelope 52" and includes transparent support strip 10" that has a length of about 7.5 centimeters, a width of about 0.9 centimeter and a thickness of about 0.8 millimeter. Measurement assembly 80 at one end of support strip 10" includes structure that defines a metering channel 16" with a rectangular inlet port 74' that is about 1.9 millimeters in width and about 0.3 millimeter in height and vent port 72' (Fig. 10) of the same dimensions. The side walls of channel 16" are defined by channel bounding members 84, 86, each of polyester based double coated adhesive medical tape (Type No. 193—Minnesota Mining and Manufacturing) that has a thickness of about 0.3 millimeter. The shape of channel 16" may be adjusted by use of other tape thicknesses. Each member 84, 86 (Fig. 11) has spaced planar inlet and outlet channel bounding surfaces 22" that are connected by an arcuate recess surface 88. Members 84, 86 are disposed on support 10" so that surfaces 22" are spaced 1.9 millimeters apart. The arcuate recess surfaces 88 define a circular analysis region 82 of about 4.4 millimeter diameter. Seated on and secured to the double-sided adhesive strip members 84, 86 is a laminate reagent assembly 40" that includes a hydrophilic synthetic fiber mesh filter layer 42" (Celanese Corporation "Celguard") having openings of about 0.2 — 0.4 micron size and a thickness of about 0.02 millimeter; an intermediate titanium dioxide-gelatin reflector layer 90 of about 0.05 millimeter thickness; and a reagent layer 44" of less than 0.02 millimeter thickness. The titanium dioxide-gelatin reflector layer 90 and the reagent-gelatin layer 44" are cast on the filter layer 42" and provided in an elongated strip 64' from which reagent assemblies 40" may be severed to provide individual reagent assembly elements, each having a length of about 0.9 centimeter. Opaque adhesive vinyl strip 48" overlies laminate assembly 40" and has a circular viewing window 50" of about 0.4 centimeter diameter which exposes the upper surface of reagent layer 44" over metering channel 16". In this particular embodiment, metering channel 16" has a total of about 7.2 microliters. As indicated in Fig. 11, channel bounding members 84, 86 and cover strip 48" may be supported on and adhesively removed from carrier strips 92 and 94 respectively.

The analytical devices shown in Figs. 6—11 are used in manner similar to that of the analytical device of Figs. 1—5, the inlet end 74, 74' of metering channel 16', 16" being touched to the drop of blood or other liquid to be analyzed and that liquid being metered into the channel by capillary action and positioned in alignment with viewing window 50', 50" for interaction with reagents in layer 44', 44" and measurement as with reflection densitometry.

The reagent layer in each of these embodiments may take a variety of forms depending on the type of analysis, and may be separated from the metering channel by more than one intervening layer, and, for example, may interact with a constituent of the liquid to be analyzed or a reaction product of that constituent. Various types of analysis techniques may be utilized including, for example, reaction rate and end point types of analyses. The components of any particular layer will depend on the use for which the analytical device is intended.

Thus a sample may be taken by a unitary analytical device of the invention itself with the inducted sample being visible on one side of the device and the reaction results available on the opposite side. The analytical devices can be adapted for use in carrying out a wide variety of chemical analyses and are particularly useful in the field of clinical chemistry and for the testing or analysis of biological fluids where test results are available shortly after sample is taken.

CLAIMS

1. A device for analysis of biological fluids and the like comprising support structure for manual manipulation, laminate structure on said support structure, said laminate structure including a reagent layer that comprises reagent material in a supporting matrix, and a filter layer on one side of said reagent layer, said reagent material being specifically reactable with a constituent of interest of the fluid to be analyzed, and structure defining a self-filling metering channel of capillary dimension, said metering channel being bounded in part by said filter layer and in part by said support structure, such that metering channel is in selective communication with said reagent material through said filter layer.

2. The device of claim 1 wherein said metering chann l has an inl t end and a vent port spaced from said inlet end.

3. The device of claim 1 and further including tip structur for contact with the fluid to b analyzed projecting from the inlet end of said metering channel.

4. The device of any one of claims 1—3 and further including a distribution region as part of said metering channel.

5. The device of claim 4 wherein said distribution region includes an area on either side of a central metering channel region, each said distribution area being in the form of a channel of less depth than said central metering channel region.

6. The device of claim 1 wherein said laminate structure further includes a reagent viewing region on the side of said reagent layer opposite said filter layer.

7. The device of claim 6 wherein said laminate structure includes reflective means adjacent the side of said reagent layer facing said filter layer, said reflective surface means reflecting radiation that is incident on said reagent layer at said reagent viewing region through said viewing region for detection by measuring apparatus.

8. The device of either claim 1 or 7 wherein said filter layer is of polymeric material and has pores of less than one micron size.

9. The device of any one of claims 1—3 wherein said reagent material comprises glucose oxidase, peroxidase, and an indicator composition comprising a compound oxidizable in the presence of hydrogen peroxide and peroxidase to effect formation of a dye.

10. The device of claim 1 and further including a protective member in overlying relation to said laminate structure, said protective member having a reagent viewing region therein.

11. The device of any one of claims 1—3 wherein the volume of said metering channel is less than ten microliters.

12. The device of claim 1 wherein said support structur is transparent so that the position of the sample to be analyzed in said metering channel may be viewed.

13. The device of claim 12 for whole blood analysis wherein said filter layer is of polymeric material and has pores of less than one micron size.

14. The device of claim 13 wherein said reagent material comprises glucose oxidase, peroxidase, and an indicator composition comprising a compound oxidizable in the presence of hydrogen peroxide and peroxidase to effect formation of a dye.

15. The device of claim 14 and further including a protective member in overlying relation to said laminate structure, said protective member having a reagent viewing region therein, and wherein said laminate structure includes reflective means adjacent the side of said reagent layer facing said filter layer for reflecting a beam of incident radiation that impinges on said reagent viewing region and passes through said reagent layer to analysis apparatus disposed on the same side of said laminate structure as said protective member.

16. The device of claim 15 including structure defining a distribution channel of less depth than said metering channel extending along either side of said metering channel to assist in distribution of components of whole blood in the region of measurement.

17. The device of claim 15 or 16 wherein the volume of said metering channel is less than ten microliters.

18. The device of claim 17 wherein said metering channel has an inlet end and a vent port spaced from said inlet end and including tip structure for contact with the fluid to be analyzed projecting from the inlet end of said metering channel.

19. A device for the analysis of biological fluids constructed and arranged to operate substantially as hereinbefore described with reference to and as illustrated in the accompanying drawings.

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